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# Model Validity and Risk of Bias in Randomised Placebo-Controlled Trials of Individualised Homeopathic Treatment

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## ABSTRACT

**Background:** To date, our programme of systematic reviews has assessed randomised controlled trials (RCTs) of individualised homeopathy separately for risk of bias (RoB) and for model validity of homeopathic treatment (MVHT). **Objectives:** The purpose of the present paper was to bring together our published RoB and MVHT findings and, using an approach based on *GRADE* methods, to merge the quality appraisals of these same RCTs, examining the impact on meta-analysis results. **Design:** Systematic review with meta-analysis. **Methods:** As previously, 31 papers (reporting a total of 32 RCTs) were eligible for systematic review and were the subject of study. **Main outcome measures:** For each trial, the separate ratings for RoB and MVHT were merged to obtain a single overall quality designation ('high', 'moderate', 'low', 'very low'), based on the *GRADE* principle of 'downgrading'. **Results:** Merging the assessment of MVHT and RoB identified three trials of 'high quality', eight of 'moderate quality', 18 of 'low quality' and three of 'very low quality'. There was no association between a trial's MVHT and its RoB or its direction of treatment effect ( $P>0.05$ ). The three 'high quality' trials were those already labelled 'reliable evidence' based on RoB, and so no change was found in meta-analysis based on best-quality evidence: a small, statistically significant, effect favouring homeopathy. **Conclusion:** Accommodating MVHT in overall quality designation of RCTs has not modified our pre-existing conclusion that the medicines prescribed in individualised homeopathy may have small, specific, treatment effects.

**Abstract word count: 239**

**Key words:** Individualised homeopathy; Meta-analysis; Model validity; Randomised placebo-controlled trials; Systematic review

## 51 BACKGROUND

52

53 Our programme of systematic reviews of randomised controlled trials (RCTs) in homeopathy is focusing  
54 its quality assessment both on internal validity (risk of bias, RoB) and on model validity (MV) [1]. Our  
55 earlier work on RoB showed that, of 32 eligible RCTs of individualised homeopathy, none was totally  
56 free from potential bias, though three comprised ‘reliable evidence’ [2]. As regards MV of the same 32  
57 RCTs, 19 were considered acceptable, nine uncertain, and four inadequate [3]. Sensitivity analysis  
58 reflecting the ‘reliable evidence’ produced cautious support for the hypothesis that the effect of the  
59 individualised homeopathic intervention is distinguishable from the same approach using placebos [2].

60

61 The purpose of the present paper is to merge together our previously published RoB and MV findings  
62 [2, 3] and, using an approach based on the *GRADE* method [4], to establish an overall quality  
63 designation for each of the 32 RCTs and to examine its impact on the sensitivity analysis findings.  
64 Inter-relationships between RoB, MV and direction of treatment effect are also explored.

65

## 66 METHODS

67

### 68 *Inclusion criteria for RCTs*

69

70 We previously applied the appraisal methods for RoB and for model validity of homeopathic treatment  
71 (MVHT), as described [1, 3, 4, 5], to papers that reported peer-reviewed, randomised, placebo-  
72 controlled trials of individualised homeopathy, published up to the end of 2013. Through formal  
73 literature search methods, and after application of defined exclusion criteria, 31 papers (reporting a total  
74 of 32 RCTs) were found to be eligible for systematic review [2].

75

### 76 *Assessment of model validity of homeopathic treatment*

77

78 For each trial, the domains for MVHT assessment are summarised as follows [3, 5]:

79

80 ***Domain I (Rationale):*** Would a significant body of accredited homeopaths support the rationale  
81 for the intervention used in the study?

**Domain II (Principles):** Is the specific intervention used consistent with homeopathic principles?

**Domain III (Practitioner):** Does the study have suitably qualified and experienced homeopathic practitioner input?

**Domain IV (Outcome measure):** Does the main outcome measure reflect the main effect expected of the intervention used?

**Domain V (Outcome sensitivity):** Is the main outcome measure capable of detecting change?

**Domain VI (Follow-up):** Is the length of follow-up for the main outcome measure appropriate to detect the intended effect of the intervention?

The overall MVHT classification per trial was assigned as follows [3, 5]:

*Acceptable MVHT:* Acceptable rationale (domain I) and principles (domain II); acceptable outcome measure (domain IV) and sensitivity (domain V); not ‘inadequate MVHT’ in either of the other two domains (III, VI).

*Uncertain MVHT:* ‘Unclear’ for at least one of the four key domains (I, II, IV, V); not ‘inadequate MVHT’ for either of the other domains (III, VI).

*Inadequate MVHT:* ‘Unacceptable MVHT’ for any one or more domains.

#### *Assessment of risk of bias*

For each trial, the domains for RoB are summarised as follows [6]:

**Domain I:** Sequence generation.

**Domain II:** Allocation concealment used to implement the random sequence.

**Domain IIIa:** Blinding of participants and study personnel.

**Domain IIIb:** Blinding of outcome assessors.

**Domain IV:** Incomplete outcome data.

**Domain V:** Selective outcome reporting.

**Domain VI:** Other sources of bias.

The overall RoB classification per trial was assigned as follows [2]:

- *Low risk of bias overall:* Low risk of bias for each of the seven domains above (designated *reliable evidence*).
- *Uncertain risk of bias overall:* Unclear RoB for at least one domain; low RoB for all other domains.
  - A trial was designated *reliable evidence* if the uncertainty in its risk of bias was for *one* of domains IV, V or VI *only* (and free of overt bias for each of domains I, II, IIIA and IIIB).
- *High risk of bias overall:* High RoB for any one or more domains.

#### *Merging RoB and MVHT into single overall quality designation*

Our separate ratings for RoB [2] and MVHT [3] were merged to obtain a single overall designation, based on the *GRADE* principle of 'downgrading' trials with lesser degrees of quality [4]. For the current study, a trial was downgraded using the specific approach shown in **Table 1**.

#### *Direction of treatment effect*

For each trial, the 'direction of treatment effect' was described statistically as 'favouring homeopathy' or 'favouring placebo', as per the findings of our previous meta-analysis [2]. These descriptions reflect, respectively, a mean odds ratio (OR) greater than or less than 1.00; statistical significance at  $P \leq 0.05$  was attributed if the 95% confidence interval (CI) did not overlap the value OR = 1.00.

#### *Inter-relationship between trial attributes*

We planned to use the Chi-squared ( $\chi^2$ ) test to compare frequencies of observations, and thus the inter-relationships between RoB and MVHT and direction of treatment effect. Fisher's Exact test was preferred when expected frequency was less than 5 in at least one cell of a given frequency table.

#### *Sensitivity analysis*

143 Sensitivity analysis, using methods corresponding to those in our associated paper [2], examined the  
144 impact on the pooled OR of trials' overall quality designation.

145

## 146 **RESULTS**

147

### 148 *MVHT overall*

149

150 As previously reported [3], there were 19 trials with acceptable MVHT, nine with uncertain MVHT, and  
151 four with inadequate MVHT (**Table 2**).

152

### 153 *RoB overall*

154

155 No trials had low RoB [2]. There were 12 trials with uncertain RoB (three of which were designated  
156 'reliable evidence': study numbers A5, A19 and A20 in Table 2), and 20 with high RoB (Table 2).

157

### 158 *Overall quality designation (Table 2)*

159

160 Each of the three trials assessed as 'reliable evidence' [2] had acceptable MVHT [3]: these three trials  
161 were therefore designated 'high quality', and so remain the top-ranked RCTs of individualised  
162 homeopathic treatment. Of the other nine trials that had uncertain RoB, eight had acceptable or  
163 uncertain MVHT, and one had unacceptable MVHT; with appropriate downgrading by quality, these  
164 trials were designated respectively as 'moderate quality' (N=8) and 'low quality' (N=1). Thus, 11 RCTs  
165 were not importantly deficient in quality overall. Of the remaining 21 RCTs, 18 were designated 'low  
166 quality' and three as 'very low quality'.

167

### 168 *Direction of treatment effect (Table 2)*

169

170 Only 22 of the 32 trials had data that were extractable for meta-analysis [2]. Fifteen of these 22 had a  
171 direction of treatment effect favouring homeopathy; seven favoured placebo.

172

### 173 *Inter-relationship between trial attributes*

174

175 MVHT and risk of bias

176

177 There was no evidence to support an association between MVHT and RoB (Fisher's Exact  $P = 0.882$ ) –

178 **Table 3.**

179

180 MVHT and direction of treatment effect

181

182 There was no evidence to support an association between a trial's MVHT and its direction of treatment  
183 effect (Fisher's Exact  $P = 0.381$ ) – **Table 4.**

184

185 Risk of bias and direction of treatment effect

186

187 There was no evidence to support an association between a trial's RoB and its direction of treatment  
188 effect (Fisher's Exact  $P = 0.690$ ) – **Table 5.**

189

190 *Sensitivity analysis*

191

192 **Table 6** shows the effect of removing data by trials' overall quality designation: i.e. removing 11 'low-  
193 quality' RCTs, then eight 'moderate-quality' RCTs. The pooled OR showed a small, statistically  
194 significant, effect in favour of homeopathy for each set of N trials, including for the final N=3 RCTs  
195 (those designated 'high quality').

196

197 **DISCUSSION**

198

199 Our study has successfully brought together RoB and MVHT assessments using an approach based on  
200 the *GRADE* system of 'downgrading' lesser-quality trials. Merging together the two quality attributes  
201 revealed 11 out of 32 trials with either high or moderate quality overall. Those with 'high quality' are  
202 the three RCTs that comprise 'reliable evidence' based on RoB [2] and that also possess acceptable  
203 MVHT [3]. The main finding from our prior meta-analysis [2] has therefore not been modified by



accommodating MVHT: there is cautious support for the hypothesis that the effect of the individualised homeopathic intervention is distinguishable from the same approach using placebos.

The trials with ‘moderate quality’ overall are eight of nine RCTs that comprise uncertain risk of bias [2]. The MVHT-deficient trial with uncertain risk of bias (study number A25) displayed a direction of treatment effect favouring homeopathy.<sup>n</sup> There was no trial that had inadequate MVHT and whose direction of effect favoured placebo, though other MVHT-deficient trials did not contain extractable data for meta-analysis, preventing their quantitative examination.

It is notable that many trials with acceptable MVHT had high RoB. Indeed, high RoB comprised the major proportion of trials in each class of MVHT (Table 3), though no statistically significant inter-relationships were evident. The proportion of trials with a given direction of treatment effect appeared to be little affected by RoB and/or MVHT; the total number of trials is too small, however, to enable definitive conclusions. The absence of such relationships is supported by our sensitivity analysis, which showed a small, significant treatment, effect toward homeopathy irrespective of the quality of trial retained in analysis. To date, therefore, there is no evidence that the MVHT method merely intercepts those trials with evidence against homeopathy, as has been suggested recently [7].

It remains a matter of concern to homeopathy that two-thirds (21 of 32) RCTs of individualised homeopathic treatment have importantly deficient quality overall. Although RCTs in conventional medicine have not benefitted from a two-attribute appraisal of quality such as ours, systematic reviews that solely examined RoB have frequently expressed concern about the insufficient quantity of evidence available to answer a given research question [8]. It is reassuring, at least, that so few of our 32 homeopathy trials have overtly inadequate MVHT [3] and that the majority thus seem to involve ‘genuine homeopathy’ [9]. It is unknown to what extent model validity might impact on the interpretation of RCT findings in other branches of Complementary/Alternative Medicine (CAM); our MVHT method seems adaptable to addressing that question, as previously proposed [5]. It is also

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<sup>n</sup> Additional sensitivity analysis based on the original authors’ selection of ‘primary outcome measure’ has identified potentially a fourth RCT in the category ‘Uncertain RoB – reliable evidence’: <http://www.britishhomeopathic.org/wp-content/uploads/2015/01/BHA-16-Jan-2015.pdf>. That RCT (White 2003: study number A39 in tabulated material) would then be upgraded in our current rank order classification – see **Supplementary File 1** – as a second trial that is MVHT-deficient and with uncertain risk of bias, displaying a direction of treatment effect favouring homeopathy: its overall designation would be ‘low quality’ rather than ‘very low quality’.

currently unknown if other potential flaws, connected with deficiencies of external validity for example [10], might impinge on overall quality ratings of the trials we examined.

In classifying each of MVHT and RoB, we considered some domains of assessment to have lesser importance than others. This judgmental approach to the relative importance of domains is consistent with the Cochrane method of attributing overall RoB per trial [6]. It preserves *PRISMA* standards of reporting, and it has successfully identified trials of individualised homeopathy that comprise ‘reliable evidence’. Similar dual assessment and analysis will feature in our subsequent systematic review of placebo-controlled RCTs of *non*-individualised homeopathy.

## CONCLUSIONS

The quality appraisal of 32 RCTs of individualised homeopathic treatment, merging the assessments of MVHT and RoB, identified three trials of ‘high quality’, eight of ‘moderate quality’, 18 of ‘low quality’ and three of ‘very low quality’. Since the three ‘high quality’ trials are those that were already identified as ‘reliable evidence’, there is no change in our main conclusion from previous meta-analysis based on the best-quality RCTs: the medicines prescribed in individualised homeopathy may have small, specific, treatment effects.

## ADDITIONAL FILES

**Supplementary file 1:** Rank order of 32 trials by overall quality designation, and showing direction of treatment effect (from meta-analysis data): if reclassifying White (2003) as ‘Uncertain RoB – reliable evidence’.

## Declaration of competing interests

RTM, JC and SM are employed by, or associated with, a homeopathy charity to clarify and extend an evidence base in homeopathy. The study is intrinsic to the charity work of the British Homeopathic Association (BHA) through its Research Development Adviser, RTM; no other member of the BHA’s staff, nor its trustees, contributed to the design, analysis or write-up of the work. Each of the following is a former member of the International Scientific Committee for Homeopathic Investigations (ISCHI): RTM, MVW, JJ, MO, JF, RJM, HR, FD, PF. The University of Glasgow was supported by a grant from the British Homeopathic Association. For activities outside the submitted study, JRTD has received

264 honoraria or royalties from a number of organisations, including universities and pharmaceutical  
265 companies.  
266

## 267 **Authors' contributions**

268 RTM devised and led the study in collaboration with all co-authors. SML, LAL, JC, SM, JRTD and IF  
269 are co-authors of the original paper on risk-of-bias [2]; MVW, JJ, MO, JF, RJM, HR, FD and PF are co-  
270 authors of the original paper on model validity [3]. Each co-author contributed to interpretation of the  
271 merged data, and edited and approved the final manuscript.  
272

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276

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**Table 1: Method for merging RoB and MVHT into single overall designation of quality**

Attribute of quality				
RoB	MVHT	Descriptive criteria for downgrading	Downgrading	Overall designation
Low risk	Acceptable	Neither attribute has important flaws	0	High quality
Uncertain risk**	Acceptable			
Uncertain risk	Acceptable	One attribute is 'uncertain'; the other attribute is 'uncertain' or better	-1	Moderate quality
Uncertain risk	Uncertain			
Uncertain risk	Inadequate	One attribute has important flaws	-2	Low quality
High risk	Acceptable			
High risk	Uncertain			
High risk	Inadequate	Both attributes have important flaws	-3	Very low quality

\*\*Includes those trials designated 'reliable evidence'.

No trial in the current study was designated 'low risk of bias' – see Results.

**Table 2: Rank order of 32 trials by overall quality designation, and showing direction of treatment effect (from meta-analysis data<sup>2</sup>)**

Ref.	First author	Year	Overall RoB	Overall MVHT	Downgrading	Overall designation	Direction of effect
A5	Bell	2004	Uncertain**	Acceptable	0	High quality	Homeopathy
A19	Jacobs	1994	Uncertain**	Acceptable	0	High quality	*Homeopathy
A20	Jacobs	2001	Uncertain**	Acceptable	0	High quality	Homeopathy
A10	Chapman	1999	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A14	Frass	2005	Uncertain	Acceptable	-1	Moderate quality	*Homeopathy
A23	Jacobs	2005a	Uncertain	Acceptable	-1	Moderate quality	Placebo
A36	Thompson	2005	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A41	Yakir	2001	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A6	Bonne	2003	Uncertain	Uncertain	-1	Moderate quality	Placebo
A11	de Lange de Klerk	1994	Uncertain	Uncertain	-1	Moderate quality	Homeopathy
A35	Straumsheim	2000	Uncertain	Uncertain	-1	Moderate quality	Placebo
A7	Brien	2011	High	Acceptable	-2	Low quality	Placebo
A9	Cavalcanti	2003	High	Acceptable	-2	Low quality	Homeopathy
A13	Fisher	2006	High	Acceptable	-2	Low quality	Homeopathy
A18	Jacobs	1993	High	Acceptable	-2	Low quality	----
A21	Jacobs	2000	High	Acceptable	-2	Low quality	----
A22	Jacobs	2005b	High	Acceptable	-2	Low quality	*Homeopathy
A24	Jansen	1992	High	Acceptable	-2	Low quality	----
A31	Rastogi (a)	1999	High	Acceptable	-2	Low quality	Homeopathy
A31	Rastogi (b)	1999	High	Acceptable	-2	Low quality	Placebo
A33	Siebenwirth	2009	High	Acceptable	-2	Low quality	Placebo
A38	Weatherley-Jones	2004	High	Acceptable	-2	Low quality	Homeopathy
A16	Gaucher	1994	High	Uncertain	-2	Low quality	----
A26	Katz	2005	High	Uncertain	-2	Low quality	----
A30	Naudé	2010	High	Uncertain	-2	Low quality	----
A32	Sajedi	2008	High	Uncertain	-2	Low quality	Placebo
A37	Walach	1997	High	Uncertain	-2	Low quality	----
A40	Whitmarsh	1997	High	Uncertain	-2	Low quality	Homeopathy
A25	Kainz	1996	Uncertain	Inadequate	-2	Low quality	Homeopathy
A1	Andrade	1991	High	Inadequate	-3	Very low quality	----
A34	Steinsbeek	2005	High	Inadequate	-3	Very low quality	----
A39	White	2003	High	Inadequate	-3	Very low quality	----

\*\* Reliable evidence. \* Homeopathy significantly superior to placebo (P < 0.05)

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Table 3: Frequency table of MVHT and RoB

Number of trials		Risk of bias			Totals
		Uncertain**	Uncertain	High	
MVHT	Acceptable	3	5	11	19
	Uncertain	0	3	6	9
	Inadequate	0	1	3	4
Totals		3	9	20	32

\*\* Reliable evidence

Table 4: Frequency table of MVHT and direction of treatment effect

Number of trials		Direction of treatment effect		Totals
		Favours homeopathy	Favours placebo	
MVHT	Acceptable	12	4	16
	Uncertain	2	3	5
	Inadequate	1	0	1
Totals		15	7	22

Table 5: Frequency table of RoB and direction of treatment effect

Number of trials		Direction of treatment effect		Totals
		Favours homeopathy	Favours placebo	
RoB	Uncertain**	3	0	3
	Uncertain	6	3	9
	High	6	4	10
Totals		15	7	22

\*\* Reliable evidence

**Table 6: Sensitivity analysis by overall quality designation**

Ref.	First author	Year	Overall designation	OR [95%CI]	Pooled OR [95% CI] for N trials	N trials included	P for N trials
A5	Bell	2004	High quality	1.77 [0.66, 4.72]	1.98 [1.16, 3.38]	3	0.013
A19	Jacobs	1994	High quality	2.22 [1.00, 4.94]			
A20	Jacobs	2001	High quality	1.84 [0.63, 5.36]			
A10	Chapman	1999	Moderate quality	1.98 [0.72, 5.49]	1.64 [1.24, 2.17]	11	< 0.001
A14	Frass	2005	Moderate quality	3.13 [1.10, 8.86]			
A23	Jacobs	2005a	Moderate quality	0.80 [0.25, 2.57]			
A36	Thompson	2005	Moderate quality	1.94 [0.66, 5.64]			
A41	Yakir	2001	Moderate quality	5.50 [0.96, 31.62]			
A6	Bonne	2003	Moderate quality	0.87 [0.28, 2.73]			
A11	de Lange de Klerk	1994	Moderate quality	1.67 [0.96, 2.89]			
A35	Straumsheim	2000	Moderate quality	0.80 [0.34, 1.90]	1.53 [1.22, 1.91]	22	< 0.001
A7	Brien	2011	Low quality	0.86 [0.16, 4.47]			
A9	Cavalcanti	2003	Low quality	3.50 [0.55, 22.30]			
A13	Fisher	2006	Low quality	1.33 [0.34, 5.30]			
A22	Jacobs	2005b	Low quality	3.84 [1.06, 13.90]			
A31	Rastogi (a)	1999	Low quality	1.36 [0.45, 4.10]			
A31	Rastogi (b)	1999	Low quality	0.53 [0.17, 1.69]			
A33	Siebenwirth	2009	Low quality	0.49 [0.07, 3.65]			
A38	Weatherley-Jones	2004	Low quality	1.47 [0.62, 3.47]			
A32	Sajedi	2008	Low quality	0.55 [0.09, 3.34]			
A40	Whitmarsh	1997	Low quality	1.72 [0.69, 4.34]			
A25	Kainz	1996	Low quality	1.41 [0.45, 4.45]			

**Additional File 1: Rank order of 32 trials by overall quality, and showing direction of treatment effect (from meta-analysis data): if reclassifying White (2003) as ‘Uncertain RoB – reliable evidence’ (see also <http://www.britishhomeopathic.org/wp-content/uploads/2015/01/BHA-16-Jan-2015.pdf>)**

Ref.	First author	Year	Overall RoB	Overall MVHT	Downgrading	Overall designation	Direction of effect
A5	Bell	2004	Uncertain**	Acceptable	0	High quality	Homeopathy
A19	Jacobs	1994	Uncertain**	Acceptable	0	High quality	*Homeopathy
A20	Jacobs	2001	Uncertain**	Acceptable	0	High quality	Homeopathy
A10	Chapman	1999	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A14	Frass	2005	Uncertain	Acceptable	-1	Moderate quality	*Homeopathy
A23	Jacobs	2005a	Uncertain	Acceptable	-1	Moderate quality	Placebo
A36	Thompson	2005	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A41	Yakir	2001	Uncertain	Acceptable	-1	Moderate quality	Homeopathy
A6	Bonne	2003	Uncertain	Uncertain	-1	Moderate quality	Placebo
A11	de Lange de Klerk	1994	Uncertain	Uncertain	-1	Moderate quality	Homeopathy
A35	Straumsheim	2000	Uncertain	Uncertain	-1	Moderate quality	Placebo
A7	Brien	2011	High	Acceptable	-2	Low quality	Placebo
A9	Cavalcanti	2003	High	Acceptable	-2	Low quality	Homeopathy
A13	Fisher	2006	High	Acceptable	-2	Low quality	Homeopathy
A18	Jacobs	1993	High	Acceptable	-2	Low quality	----
A21	Jacobs	2000	High	Acceptable	-2	Low quality	----
A22	Jacobs	2005b	High	Acceptable	-2	Low quality	*Homeopathy
A24	Jansen	1992	High	Acceptable	-2	Low quality	----
A31	Rastogi (a)	1999	High	Acceptable	-2	Low quality	Homeopathy
A31	Rastogi (b)	1999	High	Acceptable	-2	Low quality	Placebo
A33	Siebenwirth	2009	High	Acceptable	-2	Low quality	Placebo
A38	Weatherley-Jones	2004	High	Acceptable	-2	Low quality	Homeopathy
A16	Gaucher	1994	High	Uncertain	-2	Low quality	----
A26	Katz	2005	High	Uncertain	-2	Low quality	----
A30	Naudé	2010	High	Uncertain	-2	Low quality	----
A32	Sajedi	2008	High	Uncertain	-2	Low quality	Placebo
A37	Walach	1997	High	Uncertain	-2	Low quality	----
A40	Whitmarsh	1997	High	Uncertain	-2	Low quality	Homeopathy
A39	White	2003	Uncertain**	Inadequate	-2	Low quality	Homeopathy
A25	Kainz	1996	Uncertain	Inadequate	-2	Low quality	Homeopathy
A1	Andrade	1991	High	Inadequate	-3	Very low quality	----
A34	Steinsbekk	2005	High	Inadequate	-3	Very low quality	----

\*\* Reliable evidence. \* Homeopathy significantly superior to placebo (P < 0.05)